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"Potentially, gene therapy would be much cheaper than many other current treatments"

Interview with Federico Mingozzi, Chief Scientific Officer at Spark Therapeutics, leader company in gene therapy, who was invited by CBATEG to give a seminar entitled “Developing Gene Therapies for Rare Diseases, a History of Synergy Between Academia and Industry”.

Federico Mingozzi had worked on research projects at the CBATEG laboratory of Professor Fàtima Bosch and is currently the Chief Scientific Officer of Spark Therapeutics, a company focused on the development of gene therapies for hereditary retinal, neurodegenerative and liver diseases.

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What is gene therapy?

It is a relatively new therapeutic modality, or a new, let's say, class of therapeutics that consists of using a nucleic acid that is delivered in different ways, usually with a vector derived from a virus, to treat a disease. The first class of diseases that has been targeted with gene therapy is the obvious target: genetic diseases where basically a gene is not working. It is then replaced with a

working version of the same gene delivered via a virus.

What therapies are you developing in Spark Therapeutics?

Spark has a pipeline with several different products in development. The separation of the pipeline is based on the target tissue. In opthamology we have one product whose brand name is Luxturna™. It was approved by the FDA at the end of 2017 and now is being reviewed also by the EMA in Europe. And then we have additional indications, which are always genetic diseases, affecting the retina. One of them is the Leber hereditary optic neuropathy, which is a genetic form of retinopathy due to mutations on mitochondrial genes. We also have an open clinical trial for a form of an inherited retinal disease called choroideremia. And then we have a programme on neurodegenerative diseases where we have been working on a form of lysosomal storage disease called Batten disease. It is one of the subforms of Batten disease affecting children, so we are developing a therapy for that. And we are also working on Huntington disease, which is a neurodegenerative disease. And in the liver platform, where we target the liver to treat different diseases, we have a programme on haemophilia B, in collaboration with Pfizer, which is entering phase 3 now, and we have a phase 1-2 trial on haemophilia A, and a preclinical programme on Pompe disease.

Luxturna™ is said to be the most expensive therapy on the market. Will gene therapies' prices decrease?

Luxturna is an expensive therapy, but it is not the most expensive drug available. The price of gene therapy drugs will be determined by multiple factors. One of them is how much it costs to make these types of drugs. Presumably, the cost of that may be decrasing as we become better in manufacturing gene therapy products. But then it is also a function of the market size and what disease you are trying to treat. In the future, I hope the price will decrease as the tecnology improves.

How much?

It is a very complex question. If we look at some of the enzyme replacement therapies existing today, for example the current treatment for Pompe disease, one adult patient can cost up to one million euros per year. And the same goes for the current treatment for haemophylia, with a cost of maybe 100,000 to 200,000 euros per year, for a lifetime. The price is really high with the current medication. If you consider that gene therapy is only one treatment and only once in a lifetime, even if it seems very expensive, potentially it would be much cheaper than many other current treatments. There is a lot of discussion around pricing and there is also a discussion to develop different modalities of reimbursement. One of them is to establish an alternative to paying the whole price, where one can choose yearly payments based on how long the treatment will perform.

Is gene therapy safe?

The vectors we use today for gene therapy are remarkably safe. So far, with the newer generation of vectors, we have not had any severe adverse events associated with vector related toxicities. At the end of the 1990s one person died after gene therapy, but that patient received a vector that is no longer used. It was an adenoviral vector and now we have switched to safer

vectors. We are not saying that gene therapy is free of risks. What we need to do, now that we have a lot of patients who have been treated, is to monitor them for a long time and see what is the true safety profile of these vectors. I think that the technology is evolving and there is a lot of work around non-viral gene transfer, using artificial nanoparticles, and so on. But one should always remember that each new technology will carry a new set of potential risks. What we have now seems actually fairly safe. We must see the new generation of technologies and the long-term effects of gene therapy, but so far it is remarkably safe.

There is an ethical debate about the use of gene therapy beyond the treatment of diseases. For instance, Liz Parrish, from BioViva, injected herself with a "gene-therapy" with anti-ageing effects. What is your position on this debate?

There is a lot of discussion around the "do your own" gene therapy, people trying to access gene therapy for self-administration. I think it is important for people to know that this is dangerous for a number of reasons. The first one is that you basically turn yourself into an experimental animal, so that's crazy! Parrish injected herself with a vector expressing something that can produce tumours. I would not do it to myself, to be honest. There are multiple problems. The products they have been using have not been produced with the standards needed for clinical use. So they usually are produced in uncertified facilities. And that is very dangerous because there is a risk of contaminants present in the vector preparations which can be harmful. The second reason is that it is very bad for the field of gene therapy to have trials that are not controlled and that are not properly designed. Gene therapy for telomerase is potentially very good, but she did not do the right things. She may end up with a big side effect which would kill any possibility of developing a product which could be beneficial for people. Basically, this is not the way to advance science, this is the way to kill science.

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